

REMARKS

Applicants respectfully request continued examination and reconsideration of the pending claims in view of the following remarks.

1. Status of the claims

Claims 8-11, 21, and 30-35 are pending. Claims 8-11 and 30-32 are withdrawn. Claims 1-7, and 12-20 are cancelled. Claims 33-35 stand pending and rejected.

2. Rejection of the Claims Under 35 U.S.C. § 103(a)

2.1 Claims 33 and 34

Claims 33 and 34 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Blaine (U.S. Pat. No. 4,652,549) in view of Gomez et al. (*Science* 276(5313): 800-806, 1997) and further in view of Baker et al. (*Am. J. Physiol. Heart Circ. Physiol.* 259: H324, 1990, Abstract). The Office asserts that “Blaine teaches method of treatment of cardiac hypertrophy using atrial natriuretic peptide (ANP) and fragments thereof. *See* abstract, summary, col. 3, lines 11-20, and claims 1-8. In particular, the treatment reverses cardiac hypertrophy and reduces heart weight – *see* Example 11, col. 4, lines 23-41. Thus, the reference teaches method of reducing heart weight after cardiac hypertrophy.” Office Action, pages 2-3. The Office relies on Baker in support for the argument that a decrease in heart weight demonstrated in Blaine would indicate reduction in ventricular weight. Office Action, pages 3-4. The Office relies on Gomez at page 804 for purportedly stating that “[a]s for treating cardiac hypertrophy occurring during ‘chronic cardiac dysfunction which produces pulmonary congestion’, both pulmonary congestion and cardiac hypertrophy are common signs of heart failure.”

Applicants traverse the rejection of claims 33 and 34. Turning to Blaine, Applicants assert that the allegation that a reduction of water content in the heart is not the same as a reduction of heart mass. In Blaine’s Example 11, all that is depicted is that heart weight as measured by grams H₂O per 100 grams tissue was measured. Reduction of water weight differs from a reduction in heart mass. For example, the Office cites Baker et al (1990) in support of Example 11 of Blaine being directed to a loss of heart mass. Baker does not support this contention. Baker refers to ventricle weight, but not its water content. As

illustrated in Figure 1 (page H327) of Baker, left ventricular weight is total grams measured as a ratio of left ventricular-to-body weight ratios. This is not the same assay as set forth in Blaine's Examine 11. The complete reference of Baker discusses changes in the left ventricular mass to body weight ratios. Baker does not suggest a relationship between ventricle weight and water content. Thus, Blaine's teachings of loss of water weight is not equivalent to loss of cardiac weight let alone reduction of ventricular heart mass.

Applicants attach the reference by Angelino Calderone et al., "Pressure- and Volume-Induced Left Ventricular Hypertrophies are Associated With Distinct Myocyte Phenotypes and Differential Induction of Peptide Growth Factor mRNAs," *Circulation* 92(9): 2385-2390 (1995). In the abstract of this article, the authors point out that chronic pressure and volume overload result in morphologically and functionally distinct forms of myocardial hypertrophy. The authors tested the hypothesis that the induced left ventricular hypertrophies are associated with distinct molecular phenotypes and patterns of peptide growth factor induction. Specifically, concentric hypertrophy (e.g., secondary to aortic constriction) is characterized by an increase in ventricular wall thickness, little or no chamber dilation, and the parallel addition of sarcomeres. Eccentric hypertrophy (e.g., arteriovenous shunting) is characterized by relatively little increase in wall thickness, a disproportionably large increase in chamber volume, and the serial addition of sarcomeres. Thus, the two are distinguishable. In view of the background provided by the Calderone article, it is clear that Blaine does not teach the subject matter of the pending claims.

Applicants further note that Baker is directed to the study of an unrelated angiotensin-converting enzyme inhibitor, enalapril maleate, for the study of *prevention* of left ventricular hypertrophy. "Prevention" cannot suggest that the left ventricular mass, which has been once increased, is now decreased. Prevention just means the inhibition of heart mass increase. In fact, Baker's assay had the enzyme inhibitor administered 2 days before the operation, which does not suggest at all that the ventricle weight which was once increased, has now been decreased. It only shows prevention of an initial increase.

Rejections under 35 U.S.C. §103 cannot be inherent. Inherency is immaterial in an obviousness analysis if the record establishes that one of ordinary skill in the art would not appreciate or recognize the inherent feature. *In re Shetty*, 195 U.S.P.Q. 753 (C.C.P.A. 1977). That which may be inherent is not necessarily known, and obviousness cannot be predicated on what is unknown. *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966). A

retrospective view of inherency is not a substitute for some teaching or suggestion in the prior art supporting an obviousness rejection. *In re Newell*, 13 U.S.P.Q.2d 1248 (Fed. Cir. 1989). No where does the discussion of reduction of ventricular weight occur in Blaine. The Office has not posited a scientifically reasoned position as to why the data presented in Example of 11 of Blaine must mean that the reference teaches reduction of ventricular heart mass after cardiac hypertrophy.

Next, Applicants point out that the Office's citation to Gomez at page 804 is in error. The specifically quoted material is not present and there is no sentence on page 804 that discusses this concept. The Office asserts that Gomez in combination with Blaine would render the claims obvious, because Blaine generally addresses cardiac hypertrophy and would be applicable to hypertrophy occurring during "chronic cardiac disfunction [*sic*] which produces pulmonary congestion." Applicants disagree with the Office's conclusion of the Office. Gomez is directed to hypertrophy related to systolic dysfunction. *See, e.g.*, p. 801, middle column, last paragraph. Systolic dysfunction is associated with dilated congestive cardiomyopathy. The pathology of this heart condition is characterized by an increases size in all four heart chambers. The heart wall is thinned but the heat mass remains the same. Thus, the condition discussed in Gomez is not the same as that of claims 33 and 34. The reference is misapplied and provides no weight to the Office's arguments or conclusions.

The references simply cannot be combined. Gomez relates to a different condition. Baker discussed changes in the mass of the left ventricle as discussed above, which is not discussed in Blaine. The gaps in Blaine cannot be explained by Gomez. While Blaine is alleged to teach hypertrophy generally, when viewed as a whole, including Example 11, it is directed to water loss in the heart. Baker and Gomez address two different cardiomyopathies. Importantly, Gomez does not suggest whatsoever that pulmonary congestion that has occurred once is reduced with the administration of a natriuretic peptide. Given the differences in treatment as between the different types of cardiomyopathies, the combination of references does not become obvious to try. *See Takeda Chemical Industries Ltd. v. Alphapharm Pty Ltd.*, 83 U.S.P.Q.2d 1169, 1176-77 (Fed. Cir. 2007). It remains today that there must be evidence in the combination that provides an expectation of success. The differences in hypertrophy fail to provide that expectation of success such that the

combination of Blaine-Gomez-Baker renders claims 33 and 34 obvious. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Applicants further note that the Office has not applied anew the references of Espinar, Tilley and Cao against claims 33 and 34. Applicants conclude that the claims are free of the teachings of these references.

2.2 Claim 35

Claim 35 stands rejected under 35 U.S.C. § 103(a) allegedly as being unpatentable under 35 U.S.C. §103 (a) as obvious over Blaine in view of Gomez et al. and further in view of Baker et al. as applied to claims 33, 34 above, and further in view of Saito et al. (not Salito) (*Circulation*, 76: 115-124, 1987). In a conversation with the Examiner held August 28, 2007, the rejection was clarified and the recitation of “33-34 are rejected” in the first 2 lines of paragraph no. 3 on page 4 of the Office Action were unintended. Saito is relied upon by the Office only for the purported teaching that BNP is a functional equivalent of ANP.

The combination of Blaine, Gomez, and Baker fail for the reasons discussed above. The basis for which the Office relies on Saito does not cure the defects of the Blaine-Gomez-Baker combination. Therefore, Applicants assert that no *prima facie* case of obviousness has been adduced. The rejection should respectfully be withdrawn.

Applicants further note that the Office has not applied anew the references of Espinar, Tilley and Cao against claim 35 as it had in the prior Office Action. Claim 35 is rejected under a different combination of references. Thus, Applicants conclude that the claims are free of the teachings of these references.

CONCLUSION

In view of the foregoing, Applicants respectfully request the entry of the amendments to place the application in condition for allowance, or in the alternative, in better form for appeal.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0573. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is respectfully requested and the fee should also be charged to our Deposit Account

If any matters remain outstanding, the Examiner is invited to contact the undersigned representative regarding this matter.

Respectfully submitted,
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